The Impact of Prehospital Tranexamic Acid on Blood Coagulation in Trauma Patients

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Abstract: BACKGROUND: here is limited data on prehospital administration of tranexamic acid (TXA) in civilian trauma. The aim of this study was to evaluate changes in coagulation after severe trauma from on-scene to the hospital after TXA application in comparison to a previous study without TXA. METHODS: he study protocol was registered at ClinicalTrials.gov (NCT02354885). A prospective, multicenter, observational study investigating coagulation status in 70 trauma patients receiving TXA (1 g intravenously) on-scene versus a control group of 38 patients previously published without TXA. To account for potential differences in patient and trauma epidemiology, crystalloid and colloidal resuscitation fluid, 2 propensity score matched groups (n = 24 per group) were created. Measurements included ROTEM, standard coagulation tests and blood gas analyses on-scene and emergency department admission. Presented values are mean and [standard deviation], and difference in means and 95% confidence intervals. RESULTS: atient epidemiology was not different between groups. Coagulation assays on-scene were comparable between the TXA and C. Prehospital hyperfibrinolysis was blunted in all 4 patients in the TXA group. Viscoelastic FIBTEM maximum clot firmness (MCF), representing functional fibrinogen levels, did not change from on-scene to the emergency department in the TXA group, whereas MCF decreased -3.7 [1.8] mm in the control group. Decrease of MCF was significantly reduced in the TXA group in EXTEM by 9.2 (7.2-11.2) mm ($P < .001$) and INTEM by 6.8 (4.7-9.0) mm ($P < .001$) in favor of the TXA group. Production of fibrinogen fragments (represented by D-dimers) was significantly lower in the TXA group compared to group C. CONCLUSIONS: arly prehospital administration of TXA leads to clot stabilization and a reduction of fibrinolytic activity, causing a decrease in fibrin degradation products buildup (D-dimer).

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The Impact of Prehospital Tranexamic Acid on Blood Coagulation in Trauma Patients

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BACKGROUND: There is limited data on prehospital administration of tranexamic acid (TXA) in civilian trauma. The aim of this study was to evaluate changes in coagulation after severe trauma from on-scene to the hospital after TXA application in comparison to a previous study without TXA.
METHODS: The study protocol was registered at ClinicalTrials.gov (NCT02354885). A prospective, multicenter, observational study investigating coagulation status in 70 trauma patients receiving TXA (1 g intravenously) on-scene versus a control group of 38 patients previously published without TXA. To account for potential differences in patient and trauma epidemiology, crystalloid and colloidal resuscitation fluid, 2 propensity score matched groups (n = 24 per group) were created. Measurements included ROTEM, standard coagulation tests and blood gas analyses on-scene and emergency department admission. Presented values are mean and [standard deviation], and difference in means and 95% confidence intervals.
RESULTS: Patient epidemiology was not different between groups. Coagulation assays on-scene were comparable between the TXA and C. Prehospital hyperfibrinolysis was blunted in all 4 patients in the TXA group. Viscoelastic FIBTEM maximum clot firmness (MCF), representing functional fibrinogen levels, did not change from on-scene to the emergency department in the TXA group, whereas MCF decreased −3.7 [1.8] mm in the control group. Decrease of MCF was significantly reduced in the TXA group in EXTEM by 9.2 (7.2–11.2) mm ($P < .001$) and INTEM by 6.8 (4.7–9.0) mm ($P < .001$) in favor of the TXA group. Production of fibrinogen fragments (represented by D-dimers) was significantly lower in the TXA group compared to group C.
CONCLUSIONS: Early prehospital administration of TXA leads to clot stabilization and a reduction of fibrinolytic activity, causing a decrease in fibrin degradation products buildup (D-dimer). (Anesth Analg 2017;XXX:00–00)

KEY POINTS

- **Question:** Are there changes in coagulation after severe trauma from on-scene to the hospital after tranexamic acid (TXA) application in comparison to a previous study without TXA?
- **Findings:** Early prehospital administration of TXA leads to clot stabilization and a reduction of fibrinolytic activity, causing a decrease in fibrin degradation products buildup (D-dimer).
- **Meaning:** Emergency medical services should use TXA in the preclinical setting to improve coagulation in severe trauma patients.

Exsanguination still remains the primary cause of early mortality in civilian trauma.[1] Recent studies have shown that acute traumatic coagulopathy aggravate bleeding.[2–4] Early clot degradation by fibrinolysis was identified as being one of the key aspects in acute traumatic coagulopathy and massive bleeding.[5] Several studies on the clinical use of the antifibrinolytic tranexamic acid (TXA) have been performed.[6] To date, there is only 1 large randomized controlled trial, the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH-2), where the in-hospital administration of TXA in trauma victims has been investigated and a positive effect on mortality was found.[7–9] Recently, the benefit of general in-hospital TXA administration to all trauma patients irrespective of the presence or absence of hyperfibrinolysis has been questioned.[10,11] Nevertheless, the current European Trauma Treatment Guidelines recommend the early use of TXA in bleeding trauma patients.[12] In addition, up to now, only few retrospective studies on the prehospital use of TXA exist[13–15] and the exact mechanism of action of early TXA administration in trauma patients is insufficiently known.

We thus performed the current prospective study in which trauma patients received 1g of TXA after the first blood sample was taken on-scene and coagulation was reassessed in the emergency department (ED) to determine the influence of TXA on the early evolution of coagulation

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after trauma; the hypothesis being that clot degradation is stopped by the early administration of TXA.

METHODS

The study was approved by the local ethics committee (Kantonale Ethikkommission Zurich, Switzerland, study number KEK-ZH 2014-0069) including the fact that subjects were exempted from providing written consent because the first blood sample was drawn under conditions in which patients could not give informed consent.[16] Once the patients were medically stabilized, they were approached to provide a delayed informed consent. In case of death, the patients' relatives were contacted. Without informed consent, all samples and data were discarded. The study protocol was registered at ClinicalTrials.gov (NCT02354885).

This multicenter prospective observational study was conducted in 3 level-1 trauma centers in Switzerland (University Hospital Zurich, Cantonal Hospitals of Lucerne, and Saint Gallen) in collaboration with the emergency medical service (EMS) of the city of Zurich (Schutz und Rettung Zurich, Zurich, Switzerland) and the helicopter EMS Rega (Swiss Air-Ambulance, Rettungsflugwacht, Garde Aérienne, Zurich Airport, Zurich, Switzerland).

The enrollment for this study was conducted between December 2014 and March 2016. Samples of the control group (no prehospital administration of TXA) were collected between April 2009 and October 2012 and previously published by Theusinger et al.[17]

Study eligibility was given for patients aged ≥18 years with severe trauma or traumatic brain injury with a national advisory committee for aeronautics score ≥3 receiving prehospital TXA after blood sampling. The national advisory committee for aeronautics score is only used for the prehospital qualification of patients and does not correlate well with the post hoc calculated injury severity score (ISS) which is used as a standard for injury classification in trauma patients. After recruiting the necessary number of patients with an ISS ≥16 (as indicated by sample size calculation), patient enrollment was stopped. For the final analysis, patients with ISS ≥9 were included. Patients were excluded if they were pregnant, <18 years of age, unable to speak 1 of the national languages, or if they denied informed consent (Figure 1).

The sample collection of the control group was previously published and described in detail by Theusinger et al.[17] In the TXA group, the initial medical treatment of patients was not delayed for study purposes. The second intravenous line, as recommended by Pre-Hospital Trauma Life Support (PHTLS), 8th edition, for severely traumatized patients, was used to collect the blood samples on-scene: 9 mL of citrated blood (S-Monovette; Sarstedt AG&Co, Nürnbrecht, Germany, containing 1 mL 3.2% trisodium citrate) and 1.7 mL in a blood gas analysis syringe (SafePICO aspirator, Radiometer Medical, Bronshoj, Denmark, containing 80 IU heparin). Thereafter, 1 g of TXA (MEDA Pharma GmbH, Wangen-Bruttisellen, Switzerland) was given intravenously. A second identical set of blood samples was drawn when the patient arrived in the ED of one of the level-1 trauma centers mentioned above.

Laboratory data acquisition consisted of blood gas samples (on-scene and ED), which were immediately analyzed by ABL 800 (Radiometer Medical, Bronshoj, Denmark) and pH, hematocrit, hemoglobin, lactate, base excess, anion gap, and bicarbonate were measured. Coagulation values included data from whole blood ROTEM (TEM International GmbH, Munich, Germany) measurements were performed within 120 minutes of blood sampling.[18] INTEM (ellagic acid activated intrinsic pathway), EXTEM (tissue factor activated extrinsic pathway), FIBTEM (containing platelet inhibitor cytochalasin D, evaluating the contribution of fibrinogen to clot formation), and APTEM (containing aprotinin to inhibit plasmin to evaluate fibrinolysis) tests were performed and maximal clot firmness (MCF) and maximal lysis (ML) were determined. The remaining citrated plasma was stored at

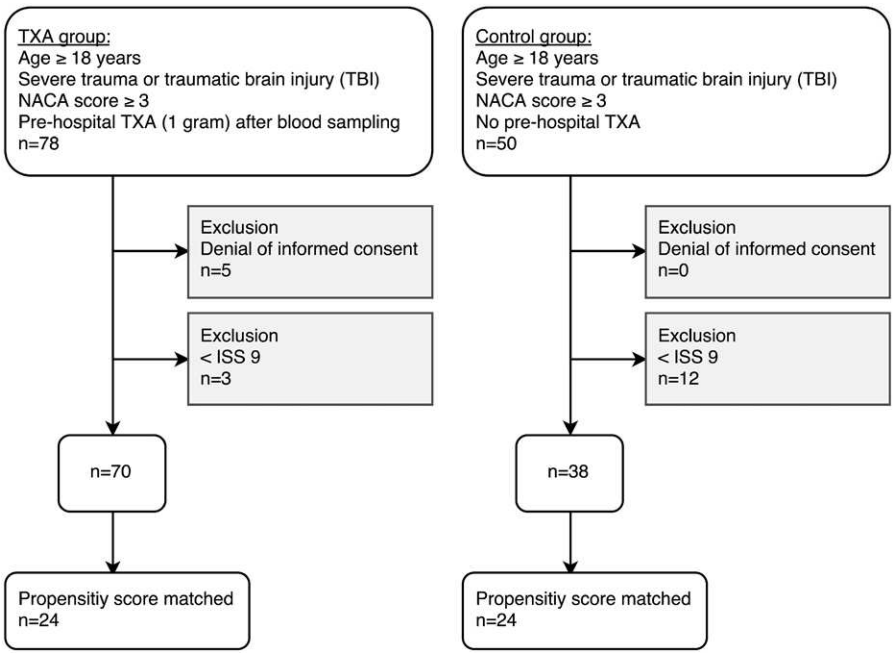

Figure 1. Flowchart of study inclusion criteria. ISS indicates injury severity score; NACA, national advisory committee for aeronautics; TXA, tranexamic acid.

–80°C and collectively analyzed in the quality controlled International Organization for Standardization (ISO) 17025 accredited central hematology laboratory of the University Hospital Zurich after the completion of the study. Assessment of international normalized ratio (INR) was determined by the Behring Coagulation System (BCS) XP (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany) using the Innovin test. Fibrinogen (Clauss method) was measured by BCS XP using Multifibrin U. FXIII activity was determined by BCS XP (Siemens Healthcare Diagnostics GmbH). Protein C activity was measured using the protein C chromo on BCS XP. D-Dimers were determined using the mini VIDAS D-Dimer Exclusion (bioMerieux, Lyon, France) test. Factor V activity was determined by BCS XP (Factor V-Dade Innovin, Siemens Healthcare Diagnostics GmbH).

Demographic data included type of trauma. ISS and anatomical-based abbreviated injury scores were documented or calculated respectively by medical encoders responsible for the annual report for the TraumaRegister database of the German Society of Trauma Surgery. Patient demographics (sex, age), vital parameters (heart rate, systolic blood pressure) at the scene and in the ED, type and quantity of resuscitation fluid were documented. Crystalloid solution used by EMS and helicopter emergency medical service (HEMS) was balanced lactated solution (Ringerfundin, B Braun Medical, Sempach, Switzerland). In the TXA group, 1 patient received colloid in the form of balanced gelatin (Physiogel balanced, B Braun Medical). In the control group, the used colloid was 6% hydroxyethyl starch (Tetraspan HES 130/0.42, B Braun).

Primary outcome was the impact of prehospital TXA on the availability of functional fibrinogen and clot stability (D-dimer production and maximum lysis indices).

Statistical Analyses

The data were entered into a spreadsheet (Microsoft Excel: Mac 2011, version 13.5.3, Microsoft Corporation, Redmond, WA). Statistical data were analyzed with IBM SPSS Statistics (version 22, IBM, Armonk, NY).

For the primary analysis, 2 propensity score matched groups (n = 24 per group) were computed using a nonparsimonious logistic regression for TXA application to account for potential differences in patient epidemiology, crystalloid and colloidal resuscitation fluid. Explanatory variables were patient age, sex, body mass index, ISS, abbreviated injury score ≥3 (head, thorax, abdomen, extremities), isolated traumatic brain injury, systolic blood pressure, heart rate, and crystalloid and colloidal fluid. Propensity score matching was performed on the logit scale with a caliper of 0.2 standard deviations of the logit of the propensity score. Standardized difference was calculated for the explanatory variables to assess the balance on base line characteristics after propensity score matching. Continuous data were presented as mean and standard deviation. The primary outcome variables related to clot degradation (difference from scene to ED) were calculated. Difference in means and 95% confidence intervals between the groups were calculated. The Mann-Whitney *U* test was used to compare continuous data between the groups and to calculate the *P* values. The Mann-Whitney *U* test was used throughout the manuscript in a unified way because of its high level of efficacy independent from data distribution. The χ^2 and Fisher exact test were used to assess the differences in categorical demographic patient data. *P* values ≤.01 were considered statistically significant. This conservative value was chosen to reduce the probability of false positive findings.

Sample Size Calculation. Based on the available data of the control group, a sample size calculation was performed to establish the study plan. This calculation intended to identify the required amount of severely injured patients (ISS ≥16) in the TXA group to detect a significant relative reduction by 50% of FIBTEM MCF decrease from the scene to the hospital compared to the control group.

RESULTS

Baseline Characteristics

A total of 108 patients with ISS ≥9 were included to the study. The TXA group consisted of 70 patients and the control group (C) of 38 patients. To account for potential differences in patient epidemiology, vital parameters, severity of trauma, body trauma region, crystalloid and colloidal resuscitation fluid, 2 propensity score matched groups (n = 24 per group) were created. The absolute standardized difference after matching was <0.20 for all explanatory variables, which confirms a valid matching (Table 1). All data presented in the manuscript are derived from the propensity score matched groups. Data including all 108 patients (unmatched) are provided in Supplemental Digital Contents 1–3, Table 1, http://links.lww.com/AA/C151, Table 2, http://links.lww.com/AA/C152, Table 3, http://links.lww.com/AA/C153.

Baseline (on-scene) blood gas values and hemoglobin value were not different between both groups (Table 2). ROTEM and coagulation assays on-scene were largely comparable between the TXA and C. However, on-scene ML of EXTEM and INTEM were significantly higher in the TXA group and factor V activity was significantly lower in the TXA group (Table 2).

Change of ROTEM Maximum Clot Firmness From On-Scene to ED

FIBTEM maximum clot firmness (MCF), representing functional fibrinogen polymerization, did not change from on-scene to the ED in the TXA group, whereas FIBTEM MCF decreased −3.7 [1.8] mm without TXA application in group C, resulting in a significant difference in means between the groups of 3.5 (2.1–4.8) mm (*P* < .001, Table 3). FIBTEM MCF difference in regard to ISS is shown in Figure 2A.

EXTEM and INTEM MCF decrease from on-scene to the ED was significantly reduced in the TXA group compared to the control group: EXTEM by 9.2 (7.2–11.2) mm (*P* < .001) and INTEM by 6.8 (4.7–9.0) mm (*P* < .001) in favor of the TXA group (Table 3).

Fibrinolysis

On-scene hyperfibrinolysis (EXTEM ML >15%) was present in 4 patients in the TXA group and 2 patients in the control group. Hyperfibrinolysis was blunted in all 4 patients in the TXA group. Reduction of ML was higher in the TXA group in EXTEM (difference in means 12% (1–24); *P* < .001) and INTEM (difference in means 9% (−3 to 22), *P* < .001) compared to group C (Table 3).

Table 1. Demographic Data of the Tranexamic Acid and Control Group

	Demographic Data			
	Propensity Score Matched Group			
	(TXA, n = 24)	(C, n = 24)		
	n (%)/Mean [SD]	n (%)/Mean [SD]	Standardized Difference	*P* Value
Age (y)	45.4 [18.9]	47.5 [21.0]	0.102	.79
Patient sex: male	20 (83%)	20 (83%)	0	>.99
BMI (kg/m^2)	25.2 [2.9]	24.8 [3.6]	0.117	.40
ISS	25 [15]	26 [17]	0.096	.79
AIS (head) ≥3	14 (58%)	15 (63%)	0.085	>.99
AIS (thorax) ≥3	8 (33%)	9 (38%)	0.087	>.99
AIS (abdomen) ≥3	3 (13%)	3 (13%)	0	>.99
AIS (extremities) ≥3	8 (33%)	8 (33%)	0	>.99
Isolated TBI	7 (29%)	6 (25%)	0.094	>.99
Systolic BP (mm Hg)	135 [29]	129 [28]	−0.154	.16
Heart rate (1/min)	85 [14]	86 [23]	0.054	.76
Crystalloid fluid (mL)	526 [366]	506 [327]	−0.058	.96
Colloidal fluid (mL)	21 [102]	45 [132]	0.194	.32

Baseline patient and trauma epidemiology of the propensity score matched groups. The *P* value (Mann-Whitney *U* test for continuous data, χ^2 test, Fisher exact test for categorical data) was calculated between the 2 groups (TXA and C). Values are expressed as mean and [SD] or number (%). Standardized difference = difference in means or proportions divided by pooled SD; imbalance defined as absolute value >0.20 (small effect size) = no imbalance in the matched groups.
Abbreviations: AIS, abbreviated injury scale; BMI, body mass index; BP, blood pressure; ISS, injury severity score; SD, standard deviation; TBI, traumatic brain injury; TXA, tranexamic acid.

Table 2. On-Scene and Emergency Department Laboratory and ROTEM Values

	On-Scene Values			ED Values		
	TXA, n = 24	C, n = 24		TXA, n = 24	C, n = 24	
	Mean [SD]	Mean [SD]	*P* Value	Mean [SD]	Mean [SD]	*P* Value
pH	7.33 [0.08]	7.33 [0.05]	.96	7.35 [0.11]	7.32 [0.07]	.36
Standard bicarbonate (mmol/L)	23.2 [2.8]	22.5 [3.5]	.53	21.8 [2.7]	22.2 [3.1]	.57
Base excess	−2.3 [2.9]	−3.0 [3.5]	.43	−3.1 [3.0]	−3.3 [3.3]	.89
Anion gap (mmol/L)	10.9 [3.9]	8.1 [4.1]	.04	8.7 [3.9]	7.2 [3.2]	.19
Hemoglobin (g/L)	151 [20]	143 [18]	.21	126 [24]	122 [26]	.53
Lactate (mmol/L)	3.3 [1.9]	2.9 [1.6]	.27	2.1 [1.5]	2.3 [1.8]	.38
EXTEM MCF (mm)	60 [7]	58 [8]	.73	61 [6]	50 [8]	**<.001**
EXTEM ML (%)	17 [26]	6 [7]	**<.001**	5 [3]	6 [6]	.54
INTEM MCF (mm)	58 [7]	57 [11]	.56	57 [6]	50 [11]	**.004**
INTEM ML (%)	18 [26]	8 [16]	**<.001**	7 [3]	6 [5]	.07
FIBTEM MCF (mm)	14 [5]	15 [4]	.46	14 [5]	11 [3.5]	**010**
FIBTEM ML (%)	10 [28]	6 [20]	.66	6 [13]	5 [6]	.23
Quick's value (%)	82 [21]	83 [17]	.89	77 [21]	85 [14]	.19
INR	1.2 [0.2]	1.1 [0.1]	.59	1.2 [0.2]	1.1 [0.1]	.14
Fibrinogen (g/L)	2.4 [1.1]	2.5 [0.7]	.34	1.9 [0.9]	2.1 [0.5]	.11
Factor XIII activity (%)	117 [24]	105 [24]	.10	100 [29]	88 [25]	.04
Factor V activity (%)	84 [25]	108 [36]	**.005**	67 [24]	93 [23]	**.001**
D-Dimers (mg/dL)	6.3 [4.8]	4.9 [4.5]	.33	6.3 [4.9]	8.8 [7.6]	.41
Protein C activity (%)	95 [20]	94 [21]	.73	84 [20]	81 [21]	.45

Mean and [SD] of the values (propensity score matched group) on-scene and in the emergency department are summarized. The *P* value (Mann-Whitney *U* test) was calculated between the groups TXA and C. *P* values ≤.01 were considered statistically significant and are printed in boldface.
Abbreviations: CFT, clot formation time; CT, clotting time; ED, emergency department; INR, international normalized ratio; MCF, maximum clot firmness; ML, maximum lysis; SD, standard deviation, TXA, tranexamic acid.

Changes in Hematology and Blood Gas Analyses From On-Scene to ED

Hematology and blood gas analyses differences from on-scene to ED were not significantly different between group TXA and C (Table 3).

Change of Coagulation Assays From On-Scene to ED

On-scene fibrinogen fragments (represented by D-dimer levels) increase with injury severity (Figure 2B). Production of fibrinogen fragments (represented by D-dimers) was significantly lower in the TXA group compared to group C (*P* = .002, Table 3, Figure 3).

The decrease of fibrinogen plasma level (Clauss method) from on-scene to ED was not different between the groups. On-scene to ED changes of coagulation factor V and XIII activity, protein C activity, Quick's value, and INR were not different between TXA and control group (Table 3).

DISCUSSION

The main findings of this study are (1) FIBTEM, EXTEM, and INTEM MCF decrease from on-scene to the ED was significantly reduced in the TXA group compared to the control group, (2) fibrinolysis is inhibited by prehospital TXA application, (3) on-scene fibrinogen fragments increase with

Table 3. Changes of Laboratory and ROTEM Values Between On-Scene and the ED

	Changes From On-Scene to ED Admission		Difference Between TXA and C	
	C, n = 24 Mean [SD]	TXA, n = 24 Mean [SD]	Difference in Means (95% CI)	*P* Value
pH	0.00 [0.07]	0.02 [0.09]	−0.02 (−0.07 to 0.03)	.43
Standard bicarbonate (mmol/L)	−0.3 [2.6]	−1.4 [2.8]	1.1 (−0.5 to 2.6)	.21
Base excess	−0.3 [2.3]	−0.8 [2.1]	0.5 (−0.8 to 1.8)	.90
Anion gap (mmol/L)	−0.9 [3.1]	−2.4 [3.1]	1.5 (−0.3 to 3.3)	.13
Hemoglobin (g/L)	−21 [27]	−25 [19]	4 (−10 to 18)	.28
Lactate (mmol/L)	−0.6 [1.3]	−1.2 [1.1]	0.6 (−0.1 to 1.3)	.03
EXTEM MCF (mm)	−8.2 [4.1]	1.0 [2.5]	−9.2 (−11.2 to −7.2)	**<.001**
EXTEM ML (%)	0 [4]	−12 [27]	12 (1–24)	**<.001**
INTEM MCF (mm)	−7.7 [4.5]	−0.8 [2.7]	−6.8 (−9.0 to −4.7)	**<.001**
INTEM ML (%)	−2 [16]	−11 [20]	9 (−3 to 22)	**<.001**
FIBTEM MCF (mm)	−3.7 [1.8]	−0.2 [2.8]	−3.5 (−4.8 to −2.1)	**<.001**
FIBTEM ML (%)	−1 [22]	−4 [31]	3 (−12 to 19)	.08
Quick's value (%)	2 [16]	−6 [17]	7 (−2 to 17)	.14
INR	0.0 [0.1]	0.0 [0.2]	−0.1 (−0.2 to 0.0)	.26
Fibrinogen (g/L)	−0.4 [0.5]	−0.5 [0.5]	0.1 (−0.2 to 0.4)	.41
Factor XIII activity (%)	−18 [18]	−17 [21]	−1 (−12 to 11)	.85
Factor V activity (%)	−15 [23]	−18 [17]	3 (−9 to 14)	.51
D-dimers (mg/dL)	3.9 [5.4]	0.1 [2.2]	3.9 (1.5 to 6.3)	**.002**
Protein C activity (%)	−13 [18]	−11 [16]	−2 (−12 to 8)	.58

Differences (propensity score matched groups) between on-scene and ED values were calculated and summarized as mean and [SD] for both groups (TXA and C). Difference in means, (95% CI), and *P* value (Mann-Whitney *U* test) of the on-scene to ED changes between the groups TXA and C were calculated. *P* values ≤.01 were considered statistically significant.

Abbreviations: C, control; CI, confidence interval; ED, emergency department; INR, international normalized ratio; MCF, maximum clot firmness, ML, maximum lysis, SD, standard deviation; TXA, tranexamic acid.

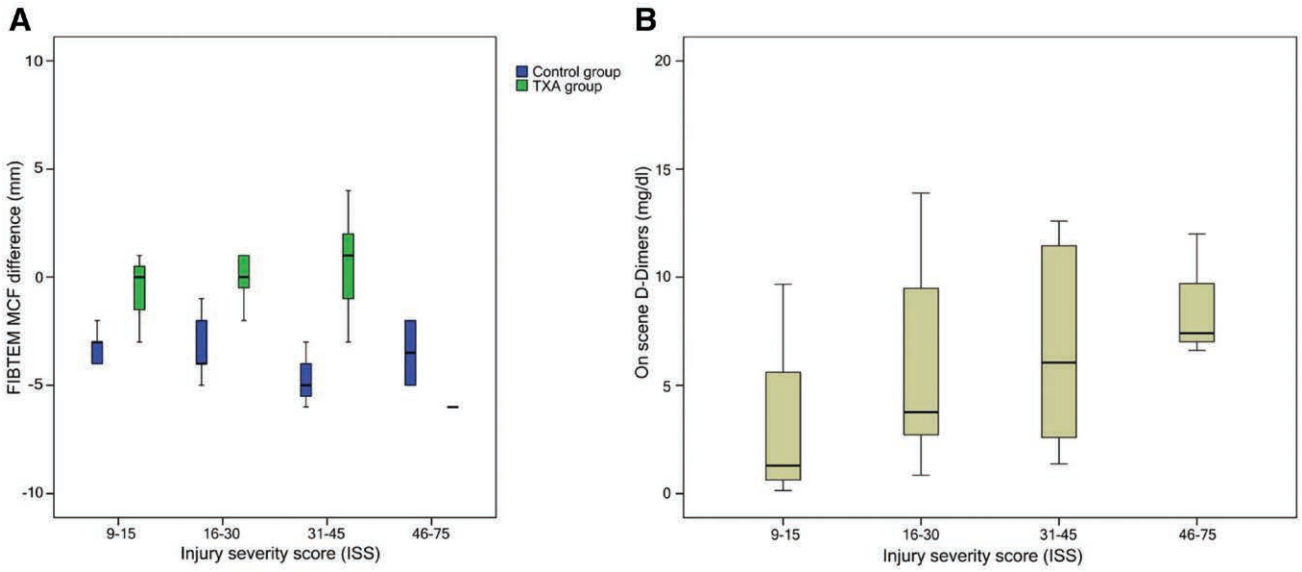

Figure 2. A, Changes of maximum clot firmness (MCF) FIBTEM between on-scene and the emergency department regarding injury severity score. FIBTEM MCF differences between on-scene and the emergency department (ED) between the groups tranexamic acid (TXA) and control (C) are displayed in regard to ISS. B, On-scene D-dimers in regard to ISS. On-scene fibrinogen fragments (represented by D-dimer levels) increase with injury severity.

injury severity, and (4) D-dimer production is significantly lower in the TXA group.

Since the CRASH-2 study,[8,9] several recommendations regarding the early use of TXA in trauma patients have been made including the latest update of the European Trauma Guidelines.[12] Only little data are available on changes of coagulation factors and rotational thromboelastometry after the administration of TXA application on-scene of trauma.[19] The study by Theusinger et al[17] regarding changes of coagulation and ROTEM in trauma patients between on-scene and the ED which served as control group showed a clear reduction of the MCF in FIBTEM, EXTEM, and INTEM as well as an increase in lysis parameters which was a clear indicator that coagulation factors are being used and that fibrinolysis was ongoing. The administration of TXA resulted in a reduced decrease of MCF in FIBTEM, EXTEM, and INTEM between on-scene and the ED and clot lysis was inhibited when patients arrived in the ED. Nevertheless, due to the ongoing blood loss, a reduction of coagulation factors could still be observed. Another argument regarding the more

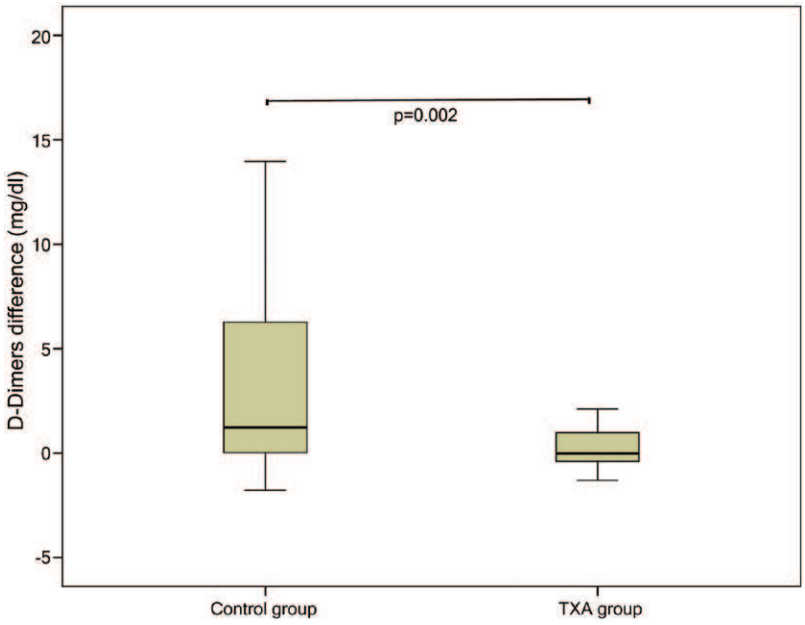

Figure 3. D-Dimers difference (on-scene to emergency department) between the groups (tranexamic acid [TXA] and control [C]). D-Dimers increase from on-scene to the emergency department was significantly lower in the TXA group compared to group C (P = .002, Mann-Whitney U test). P values ≤.01 were considered statistically significant.

stable MCF in the TXA group is that the use of colloids in the prehospital setting of trauma patients and in all other patients was abandoned since 2014 as clear evidence was published regarding the clot impairment by their use.[20] The propensity score groups were not only matched for patient demographics but also for crystalloid and colloidal resuscitation fluid.

D-Dimers, being a degradation product of fibrinogen/fibrin, is one of the few readily available standard laboratory tests as an indirect indicator of fibrinolysis/hyperfibrinolysis. The fact that the application of TXA leads to a stagnation of the D-dimer production between on-scene and the ED is clear evidence that degradation of the clot was stopped. On the other hand, we were able to show that on-scene fibrinogen fragments (represented by D-dimer levels) increase with injury severity and therefore they provide indirect information regarding the severity of trauma.[21]

Previous studies have indicated that elevated D-dimer levels are also associated with a poor outcome,[22–25] as well as the severity of tissue damage which is confirmed by our ISS correlation.[26–28] Gando et al[29] reported that high D-dimer levels on arrival at the ED indicated hyperfibrinolysis and predicted massive bleeding and death.[22–24] On the other hand, in an actual study by Hayakawa et al[21] have shown that high D-dimer levels on arrival at the ED are only a strong predictor of early death or a requirement for massive transfusion in severe trauma patients, regardless of fibrinogen levels, which may indicate hyperfibrinolytic status. The study presented in this manuscript showed that also patients with low ISSs[9–15] experience a decrease in functional fibrinogen levels from the injury scene until hospital admission which is blunted by TXA application (Figure 2A). As the inclusion criteria were along the lines with the CRASH-2 judged clinically (patients with trauma at risk for significant bleeding), also patients without numerical evidence of hemorrhagic shock might be prone to clot lysis due to released tissue plasminogen activator.

The evidence for early untargeted administration of TXA has been recently questioned by different publications.[6,10,11] A recent civilian study from the United Kingdom demonstrated that only severely injured patients in shock had a survival benefit with TXA, with a reduction in mortality from 15% to 11%.[30] Moore et al[11] were able to show in a study with 2540 patients that different phenotypes of fibrinolysis exist. The fibrinolysis shutdown phenotype was present in 46% of the patients. The mortality in that group was higher than in the group of patients with physiologic fibrinolysis. Therefore, in case of fibrinolysis shutdown, the administration of TXA might be questionable. In a study by Harvin et al,[10] TXA was administered in the ED, only after hyperfibrinolysis was proven by point of care devices. Of the 1000 patients included in their study, only 10% received TXA without effect on mortality. Based on our data, we disagree with the proposal that TXA should be administered only in the ED after hyperfibrinolysis has been proven, as we have clear indications that even in patients with a low ISS value, the production of D-dimers is stopped and clot firmness is stabilized which may represent be a benefit for patients. For the moment being, no point of care device exists which could be used to quickly guide the administration of TXA in the prehospital setting. We thus consider the "blind" TXA administration in severe trauma in the prehospital setting reasonable.

Limitations of this study need to be mentioned. The sample size was relatively small. Blood loss was neither calculated nor estimated because the data were not available for the days after the trauma. For ethical reasons, blood samples on-scene and the ED were always performed without disturbing life-sustaining treatment. This implicates that it might be possible that patients received a first dose of volume replacement before the first blood sample on-scene was drawn. Samples for blood gas analysis and the blood samples for ROTEM and laboratory analyses were drawn from a second venous access site and not cooled on ice during transportation to the ED. Several studies have

demonstrated that blood samples remain stable over a long period of time at 21°C, so we do not believe these values distort our analysis.[18,31,32] To account for differences in patient epidemiology and treatment differences in regard to resuscitation fluids, we created propensity matched groups to correct for these confounders.

In conclusion, the early administration of TXA in the prehospital setting leads to a stabilization of the clot in ROTEM, functional fibrinogen availability, and a reduction of fibrinolytic activity represented by a lower increase of D-dimer levels. Furthermore, on-scene D-dimers increase with the ISS. More studies are needed to clearly evaluate the benefit of early TXA administration as different results have actually been published.

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